

Extended Family History of Diabetes and Autoimmune Diseases in Children With and Without Type 1 Diabetes

SALLA ALHONEN, MS¹
SARI KORHONEN, MD¹
PÄIVI TAPANAINEN, MD, PHD¹

MIKAEL KNIP, MD, PHD^{2,3}
RIITTA VEIJOLA, MD, PHD¹

OBJECTIVE — To determine the extended family history of diabetes or autoimmune diseases in families with and without children having type 1 diabetes.

RESEARCH DESIGN AND METHODS — Three hundred case families and 381 control families were interviewed using structured questionnaires.

RESULTS — The proportion of case children having at least one relative with type 1 diabetes outside the nuclear family was higher than that of control children (50.3 vs. 31.8%, $P < 0.001$). The proportions of case and control children having relatives with type 2 diabetes or gestational diabetes were similar. Other autoimmune diseases occurred more frequently among the case children (9.7 vs. 1.1%, $P < 0.001$), in the case nuclear families (22.0 vs. 12.9%, $P = 0.002$) and in relatives outside the case nuclear family (72.0 vs. 62.2%, $P = 0.007$).

CONCLUSIONS — Type 1 diabetes and autoimmune diseases not only cluster in the nuclear families of children with type 1 diabetes but are also overrepresented in their extended families.

Diabetes Care 34:115–117, 2011

First degree relatives of patients with type 1 diabetes clearly have an increased disease risk (1–5), but little information is available about the occurrence of type 1 diabetes outside the nuclear family (6). It is also unclear whether type 2 diabetes and gestational diabetes are more frequently present in the families of children with type 1 diabetes (7–9). Type 1 diabetes is known to be associated with other autoimmune diseases, but there is a scarcity of data on the frequency of autoimmune diseases among other family members (10).

RESEARCH DESIGN AND METHODS

All families having a child with type 1 diabetes being treated at the Department of Pediatrics, Oulu University Hospital in September 2003 were invited to participate in this study ($n =$

306). Six families refused. The parents were interviewed, and a structured questionnaire was completed by a trained nurse (LM). Control children matched for year of birth, sex, and geographical region of residence were picked at random from the Central Population Register. The data for each family were included only once.

The families were asked about the presence of any type of diabetes in siblings, parents, and other relatives. The type of diabetes (type 1, type 2, and gestational), the age at diagnosis, and the mode of treatment (diet, medication, and insulin) were enquired. The parents were also asked about the occurrence of other autoimmune diseases in the family (celiac disease, rheumatoid arthritis, systemic lupus erythematosus, Still's disease, Sjögren's syndrome, thyroid dysfunction, hypothyroidism, hyperthyroidism, goi-

tre, psoriasis, scleroderma, ulcerative colitis, Crohn's disease, Addison's disease, multiple sclerosis, and myasthenia gravis).

We analyzed the relatives in three groups: nuclear family (the case child, siblings, and parents), extended family (nuclear family together with grandparents, siblings of parents and their children, and siblings of grandparents and their children), and extended family excluding the nuclear family.

Data analysis was performed with the SPSS for Windows statistical software (version 16.0; SPSS, Chicago, IL). The study was approved by the local ethics committee.

RESULTS — Data were obtained from 300 families with at least one child having type 1 diabetes and from 381 control families without diabetic children. The mean age of the case children at the time of data collection was 11.9 years (4.29 SD, range 1.3–19.0), and that of the control children was 12.4 years (4.33 SD, range 1.1–19.9, $P = 0.102$). The mean age of the case children at diagnosis was 6.7 years (3.87 SD, range 0.56–15.98).

The proportion of children having relatives with type 1 diabetes was higher among the case children (Table 1). No differences were found between the case and control children in the proportion having relatives with type 2 diabetes (Table 1) or in the history of gestational diabetes between the case and control mothers (8.0 vs. 8.9%, $P = 0.668$) or grandmothers (1.7 vs. 0.8%, $P = 0.290$).

Celiac disease, rheumatoid arthritis, or thyroid dysfunction had been diagnosed more often in the case children than in the control children (4.7 vs. 0.5%, $P < 0.001$; 1.3 vs. 0.0%, $P = 0.024$; 2.7 vs. 0.3%, $P = 0.006$, respectively). In addition, two case children had psoriasis and one had purpura, and one control child was diagnosed with Crohn's disease. Altogether, 9.7% of case and 1.1% of control children had an autoimmune disease other than type 1 diabetes ($P < 0.001$).

A total of 22.0% of the nuclear families of the case children had at least one family member with another autoim-

From the ¹Department of Pediatrics, University of Oulu, Oulu, Finland; the ²Hospital for Children and Adolescents and Folkhälsan Research Center, University of Helsinki, Helsinki, Finland; and the ³Department of Pediatrics, Tampere University Hospital, Tampere, Finland.

Corresponding author: Riitta Veijola, riitta.veijola@oulu.fi.

Received 8 June 2010 and accepted 20 September 2010. Published ahead of print at <http://care.diabetesjournals.org> on 27 September 2010. DOI: 10.2337/dc10-1091.

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Table 1—Proportions of children having a relative with type 1 or type 2 diabetes in their father's or mother's family

	Type 1 diabetes in given family members			Type 2 diabetes in given family members		
	Case children	Control children	P	Case children	Control children	P
n	300	381		300	381	
Father	5.0	1.3	0.005	0.3	1.6	0.111
Father's sibling(s)	5.7	2.6	0.043	3.3	5.0	0.289
Paternal cousin(s)	6.3	3.9	0.154	0.0	0.3	Not tested
Paternal grandparents	2.0	1.3	0.480	24.3	25.5	0.736
Any relative in the father's family*	31.0	16.8	<0.001	43.3	41.2	0.577
Any relative in the father's family**	28.3	16.3	<0.001	43.3	40.9	0.531
Mother	2.0	0.5	0.076	0.3	0.0	Not tested
Mother's sibling(s)	7.3	2.9	0.007	8.3	5.2	0.108
Maternal cousin(s)	8.7	3.9	0.016	0.0	0.0	Not tested
Maternal grandparents	1.3	1.3	0.981	28.7	33.1	0.218
Any relative in the mother's family*	30.0	19.4	0.001	51.0	52.5	0.699
Any relative in the mother's family**	28.7	19.2	0.004	51.0	52.5	0.699
Any relative in either the father's or mother's family	54.0	32.5	<0.001	70.3	69.8	0.884
Any relative in either the father's or mother's family**	50.3	31.8	<0.001	70.3	69.8	0.884

Data are percent. Siblings were not included in the analysis because the control children were selected to represent families without children having type 1 diabetes. None of the siblings of the case or control children had type 2 diabetes. *Extended family (parents, grandparents, siblings of parents and their children, siblings of grandparents and their children). **Extended family with the nuclear family excluded.

immune disease compared with 12.9% of the control nuclear families ($P = 0.002$). Celiac disease in particular was more common in the case nuclear families (8.0 vs. 2.9%, $P = 0.003$).

When considering extended family outside the nuclear family, a larger proportion of the case children had a positive family history of another autoimmune disease in at least one relative (72.0 vs. 62.2%, $P = 0.007$), the difference being statistically significant for rheumatoid arthritis but not for celiac disease or thyroid dysfunction (45.7 vs. 30.4%, $P < 0.001$; 31.7 vs. 28.6%, $P = 0.387$; 25.2 vs. 28.0%, $P = 0.410$, respectively).

CONCLUSIONS— This analysis of a population-based series of families of children with type 1 diabetes and control families demonstrates that type 1 diabetes or other autoimmune diseases not only cluster among the parents and siblings of the case children but also occur more often among relatives outside the nuclear family.

The strength of this study lies in the systematically collected data from case and control families in a country that has the highest incidence of type 1 diabetes in the world (11). To our knowledge, this is the first report to describe type 1 diabetes and other autoimmune diseases among relatives other than parents, siblings, or grandparents. However, the ma-

ior limitation of the study was that family history data were based on interviews only and may therefore be inaccurate.

Analysis of the maternal and paternal relatives separately yielded similar differences between the case and control children (Table 1). We confirmed that case children more often have a father than a mother with type 1 diabetes (5.0 vs. 2.0%). However, there was no such difference in the proportion of case children having at least one father's or mother's sibling with type 1 diabetes (5.7 vs. 7.3%). These observations suggest that intrauterine factors may contribute to relative protection of children of mothers with type 1 diabetes.

In children with type 1 diabetes, another autoimmune disease was observed more often than in the control children, confirming earlier reports that have showed an association between type 1 diabetes and other autoimmune diseases such as autoimmune thyroiditis and celiac disease (12–13). Juvenile rheumatoid arthritis diagnosed by a pediatrician was also more common among the case children, which is a novel finding but needs to be confirmed in a larger dataset. Interestingly, type 1 diabetes has been reported to be more frequent in children with juvenile idiopathic arthritis than could be expected on the basis of its general U.S. prevalence (14).

No differences in the occurrence of

type 2 diabetes or gestational diabetes were observed between the case and control families, which is in line with recent data showing that different genes predispose to type 1 and type 2 diabetes (15).

Acknowledgments— This study was supported by the Foundation for Pediatric Research (Helsinki, Finland), the Alma and K.A. Snellman Foundation (Oulu, Finland), and the Oulu University Hospital Research Funds.

No potential conflicts of interest relevant to this article were reported.

S.A. researched data, contributed to discussion, and wrote and edited the manuscript. S.K. researched data. P.T. and M.K. contributed to discussion and reviewed the manuscript. R.V. planned the study, researched data, contributed to discussion, and reviewed the manuscript.

The authors thank Liisa Moilanen for her careful work in data collection and the diabetes nurses at the Department of Pediatrics, Oulu University Hospital, for their skillful assistance.

References

1. Wagener DK, Sacks JM, LaPorte RE, MacGregor JM. The Pittsburgh study of insulin-dependent diabetes mellitus. Risk for diabetes among relatives of IDDM. *Diabetes* 1982;31:136–144
2. Veijola R, Reijonen H, Vähäsalo P, Sabbah E, Kulmala P, Ilonen J, Åkerblom HK, Knip M. HLA-DQB1-defined genetic susceptibility, beta cell autoimmunity, and

- metabolic characteristics in familial and nonfamilial insulin-dependent diabetes mellitus. Childhood Diabetes in Finland (DiMe) Study Group. *J Clin Invest* 1996; 98:2489–2495
3. Familial risk of type 1 diabetes in European children. The EURODIAB ACE Study Group and The EURODIAB ACE Substudy 2 Study Group. *Diabetologia* 1998;41:1151–1156
 4. Harjutsalo V, Podar T, Tuomilehto J. Cumulative incidence of type 1 diabetes in 10,168 siblings of Finnish young-onset type 1 diabetic patients. *Diabetes* 2005; 54:563–569
 5. Gillespie KM, Gale EA, Bingley PJ. High familial risk and genetic susceptibility in early onset childhood diabetes. *Diabetes* 2002;51:210–214
 6. Douek IF, Gillespie KM, Dix RJ, Bingley PJ, Gale EA. Three generations of autoimmune diabetes: an extended family study. *Diabetologia* 2003;46:1313–1318
 7. Li H, Isomaa B, Taskinen MR, Groop L, Tuomi T. Consequences of a family history of type 1 and type 2 diabetes on the phenotype of patients with type 2 diabetes. *Diabetes Care* 2000;23:589–594
 8. Douek IF, Gillespie KM, Bingley PJ, Gale EA. Diabetes in the parents of children with Type 1 diabetes. *Diabetologia* 2002; 45:495–501
 9. Barone B, Rodacki M, Zajdenverg L, Almeida MH, Cabizuca CA, Barreto D, de Araujo LF, Kupfer R, Milech A, Oliveira JE. Family history of type 2 diabetes is increased in patients with type 1 diabetes. *Diabetes Res Clin Pract* 2008;82:e1–e4
 10. Kordonouri O, Maguire AM, Knip M, Schober E, Lorini R, Holl RW, Donaghue KC, International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2006–2007. Other complications and associated conditions. *Pediatr Diabetes* 2007;8: 171–176
 11. Harjutsalo V, Sjöberg L, Tuomilehto J. Time trends in the incidence of type 1 diabetes in Finnish children: a cohort study. *Lancet* 2008;371:1777–1782
 12. Hansen D, Brock-Jacobsen B, Lund E, Bjørn C, Hansen LP, Nielsen C, Fenger C, Lillevang ST, Husby S. Clinical benefit of a gluten-free diet in type 1 diabetic children with screening-detected celiac disease: a population-based screening study with 2 years' follow-up. *Diabetes Care* 2006;29:2452–2456
 13. Kordonouri O, Klinghammer A, Lang EB, Grütters-Kieslich A, Grabert M, Holl RW. Thyroid autoimmunity in children and adolescents with type 1 diabetes: a multicenter survey. *Diabetes Care* 2002; 25:1346–1350
 14. Prahalad S, O'Brien E, Fraser AM, Kerber RA, Mineau GP, Pratt D, Donaldson D, Bamshad MJ, Bohnsack J. Familial aggregation of juvenile idiopathic arthritis. *Arthritis Rheum* 2004;50:4022–4027
 15. Raj SM, Howson JM, Walker NM, Cooper JD, Smyth DJ, Field SF, Stevens HE, Todd JA. No association of multiple type 2 diabetes loci with type 1 diabetes. *Diabetologia* 2009;52:2109–2116